PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Juha-Matti SAVOLA et al.

Serial Number: 10/534,091 Group Art Unit: 1618

Filing Date: May 6, 2005 Examiner: Gembeh, Shirley V.

For: OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jürg P. Seiler, Ph.D, ERT, hereby declare as follows:

1. I have been an independent consultant to the scientific community, to international bodies such as WHO, and to the pharmaceutical industry in the fields of non-clinical pharmacological, toxicological and regulatory issues since April 2003. Prior to 2003, I was a preclinical reviewer and head of the Toxicology Group at Swissmedic, the Swiss Agency for Therapeutic Products. My curriculum vitae is attached as Appendix I.

2. I have read and understood this application, including the claims, the Official Action dated September 11, 2009, and the references cited against the claims. U.S. Patent 5,498,623 to Karjalainen et al. ("Karjalainen et al.") and Huupponen et al., 58 Clin. Pharmacol. & Ther. 506 (1995) ("Huupponen et al."), both of which fail to disclose or suggest the QTc prolongation problem associated with oral administration of fipamezole.

3. I have reviewed and understand the three *in vivo* studies summarized in the application and discussed in detail in the Declaration by Dr. Juha-Matti Savola ("Savola Declaration"). The three studies consist of (1) a four week oral toxicity study in the dog (JSN00-1007), (2) a four week oromucosal toxicity study in the dog (JSN00-1039), and (3) a subsequent telemetered conscious dog study (JSN01-1041).

4. I have also reviewed and understand an *in vitro* safety pharmacology study on the effect of fipamezole on the hERG channel current (JSN03-1291) in HEK cells that stably express hERG. These four studies are discussed in my Expert Statement, attached as Appendix II.

5. In my opinion, the *in vitro* safety pharmacology study on cells stably expressing hERG (JSN03-1291) demonstrated the potential of fipamezole to induce prolongation of the QT interval. The effects were observed at concentrations which were in the range of the blood plasma concentrations reached in the *in vivo* toxicity studies in the dog discussed below.

6. In my opinion, the four week oral toxicity study (JSN00-1007) shows that oral administration of fipamezole induced a significant and dose-dependent prolongation of the corrected QT interval. The more fipamezole which was orally administered, the longer the QTc interval was prolonged.

7. In my opinion, one of ordinary skill in the art would have expected fipamezole to prolong the QTc interval because the concentrations of fipamezole in the blood of orally treated dogs were in the range of the *in vitro* IC_{50} value for the inhibition of hERG channel currents.

8. In my opinion, one of ordinary skill in the art would have extrapolated the QTc prolongation observed in the four week oral toxicity study in dogs (JSN00-1007) to man.

9. On information and belief, I understand the QTc prolongation problem associated with oral administration of fipamezole was unknown until the inventors discovered this problem during the course of drug development. In my opinion, such a finding would most likely lead to abandonment of the drug candidate, unless it can be demonstrated that QT interval prolongation depends on specific conditions which can be avoided in the therapeutic situation, so that the cardiac risk to patients can be minimized.

10. In my opinion, the four week oromucosal toxicity study (JSN00-1039) indicates that oromucosal administration of fipamezole does not prolong the QTc interval. Similarly, in a dog telemetry study in conscious freely-moving animals (JSN01-1041), oromucosally dosed fipamezole (buccal spray) had no effect on the ECG, thereby confirming this finding.

11. In my opinion, the JSN00-1007 and JSN00-1039 studies also show that oromucosal administration of fipamezole results in similar, if not greater, systemic exposure (C_{max} and AUC_{0-12}) than oral administration of fipamezole.

12. In my opinion, the inventors' discovery that oromucosal administration of fipamezole does not result in QTc prolongation could not have been predicted by one of ordinary skill in the art from review of Karjalainen et al. and Huupponen et al. Neither reference discloses anything about the possibility of QTc prolongation (or the lack thereof) with respect to any compound, much less suggests the problem of QTc prolongation may be minimized or eliminated by changing the mode of administration of the compound. In this regard, Huupponen et al.'s disclosure that oromucosal administration of atipamezole (a fipamezole analog) did not change heart rate (measured in beats/minute) is meaningless with respect to QTc prolongation (or the absence thereof). This is because a prolongation of the QT interval (measured in milliseconds) can be induced at unchanged heart rate, and because QTc is a value corrected for changes in, and thus independent from, heart rate. Furthermore, in my opinion, an influence of fipamezole on QTc interval could also not have been predicted from analogous effects elicited by structurally similar compounds such as atipamezole. This is because interactions of substances with the ion channels responsible for depolarization and repolarization events in cardiac tissue (such as the hERG channel) are very specific and dependent on structural properties

which can differ between homologs and derivatives of a substance to a significant extent.

13. In my opinion, the inventors' discovery that oromucosal administration of fipamezole does not result in QTc prolongation is unexpected and surprising. This is because QTc prolongation after oral administration of fipamezole is dose-dependent - the greater the amount of fipamezole orally administered, and the greater therefore its concentration in blood plasma, the greater the observed QT prolongation was. One of ordinary skill in the art, aware of the dose-dependent nature of the fipamezole oral administration problem, would expect equivalent or longer QTc prolongation if fipamezole was oromucosally administered. The fact that oromucosal administration of fipamezole does not prolong the QTc interval, despite an even greater initial amount of fipamezole in the circulating blood, is thus surprising and unexpected. In addition, there is no known case, in my opinion, of any other compound for which a change in the mode of application has eliminated a QTc prolongating effect, making the discovery even more unexpected and surprising.

14. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Signed this 4th day of December, 2009.

Jürg P. Seiler

Enclosures:

Appendix I - Curriculum vitae of Jürg P. Seiler
Appendix II - Expert Statement of Jürg P. Seiler

APPENDIX I:
CURRICULUM VITAE

Name:	SEILER, Jürg Peter
Date of birth:	January 7, 1942
Marital status:	Married, 3 children
Education:	University of Bern (Switzerland): Biochemistry Dr. phil. nat. (PhD) December 1968 1969 - 1970 Postdoctoral Fellow at NRC, Ottawa (Canada)
Present Activities:	Consulting in the fields of non-clinical pharmacological-toxicological and regulatory issues as well as in Good Laboratory Practice compliance.
Past Positions:	November 1989 – April 2003 (early retirement) Preclinical Reviewer, Head of Toxicology Group, and Head of Good Laboratory Practice (GLP) Compliance Monitoring Unit Swissmedic, Swiss Agency for Therapeutic Products, Erlachstrasse 8, CH-3000 Bern 9 (Switzerland) with the following responsibilities: Leading the Toxicology Group of Swissmedic. Evaluation of the non-clinical (pharmaco-toxicological) documentation submitted for the registration of new pharmaceutical products in Switzerland (pharmacodynamics, pharmacokinetics, toxicology) and writing the respective assessment reports. Coordination and performance of GLP inspections; international coordination with OECD and other countries' GLP Authorities. 1976 - 1989 Staff Scientist (Genetic Toxicology), Swiss Federal Research Station, CH-8820 Wädenswil 1970 - 1976 Research Fellowship (Genetic Toxicology, Research Project of the Swiss National Foundation for Scientific Research), Swiss Federal Research Station, CH-8820 Wädenswil
Memberships:	EUROTOX (since 1972) American College of Toxicology Drug Information Association European Environmental Mutagen Society Swiss Society of Toxicology Swiss Society of Laboratory Animal Science Swiss Professionals Association of Quality Assurance
Certification:	**1996: Admission to the newly formed Swiss Register of Toxicologists, consequently also registered in the EUROTOX Register of Toxicologists (EUROTOX Registered Toxicologist, ERT).** Renewal of Certification 2001 and 2006.

Special Tasks:

Genotoxicity expert for the IARC Monographs, vols. 24, 50, 53.
Swiss expert for the OECD Genotoxicity Test Guidelines (Chairman of the 1985 ad hoc Meeting)
Swiss expert in the Codex Alimentarius Committee on Pesticide Residues (until 1989)
Participation in the OECD Working Group on GLP
Swiss Expert for the Revision of the "OECD Principles of Good Laboratory Practice"
Swiss Expert for the OECD GLP Consensus Workshops on "Role and Responsibility of the Study Director" and "Multi-site Studies"
Rapporteur for the OECD Task Force on the application of the GLP Principles to in vitro studies
Chairman of the WHO/TDR Scientific Expert Working Groups on GLP and Non-Clinical Safety Testing
Toxicology Advisor for WHO/PDT (Development of malaria and tuberculosis medicines; training courses in drug development and non-clinical safety testing for scientists in disease-endemic countries)
Member of the Expert Scientific Advisory Committee (ESAC) for the Medicines for Malaria Venture (MMV)
Swiss expert (observer for EFTA) in the ICH Scientific Expert Working Group "Safety Pharmacology" (ICH Guidelines S7A and S7B)
Member of the EUROTOX Executive Committee, Member of its Subcommittee on Membership and Chairman of its Subcommittee on Publication (1993 - 1999), Member of the Subcommittee on Publication (1999 - 2001)
EUROTOX Treasurer (2002 - 2008)
Editorial Board Member of "Archives of Toxicology" (1993 – 2007)
Member of the Organising Committee of the 1987 EEMS Annual Meeting in Zurich
Member of the Organising Committee of the 1994 EUROTOX Annual Congress in Basel
Member of the Organising Committee at various DIA Workshops.

Publications:

Author and co-author of over 40 Full Papers, Reviews and Conference Abstracts in the field of Genetic and Regulatory Toxicology, and of Good Laboratory Practice
Author of a textbook on Good Laboratory Practice (Springer, 2000, 2nd edition 2005)
Editor of the EUROTOX Annual Congress Proceedings (from 1994 to 1997), Co-Editor 1999 to 2001
Co-Editor of the IUTOX Congress Proceedings (Paris, 1998)

Invited lectures and session chair at various workshops, seminars and university courses in toxicology and GLP.

ToxiConSeil
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APPENDIX II -
Expert Statement :

The importance of the oromucosal dose formulation for the cardiac safety of fipamezole

Prepared for:

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Prepared by:

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Signed:

Date and Place:

Riedtwil, December 4, 2009

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Executive Summary

The QT interval of the electrocardiogram is an important measure for the potential of a pharmaceutical substance to induce cardiac risks. Prolongation of this interval is associated in humans to serious adverse events such as ventricular tachyarrhythmia, torsade de pointes and cardiac arrest. Within the last years a number of registered drugs have been withdrawn from the market because of the cardiac risk associated with this effect of QT interval prolongation. Consequently, determining the potential of a substance to exhibit this property is of utmost importance, and this is addressed in the non-clinical development programme in various ways. Safety pharmacology studies employing *in vitro* systems, such as the hERG assay, as well as *in vivo* ECG measurements in safety pharmacology and during toxicity studies are thus mandatory. Especially, high emphasis is placed on the accurate assessment of this parameter by using telemetry to study the ECG in the conscious freely moving dog.

Safety pharmacology and toxicity studies conducted *in vitro* and in the dog *in vivo* have thus been conducted with fipamezole in order to characterize the potential hazard of QT interval prolongation. The *in vitro* hERG assay, in which the inhibition of the potassium current through the hERG channel is investigated under the influence of the drug, demonstrated the potential of fipamezole to inhibit this current to 50% of its control value (IC_{50}) at a concentration of 2.2 µg/ml. In a 4 week toxicity study with oral administration of the drug, a significant and dose-dependent prolongation of the QT interval, corrected for the heart rate (QTc), was observed at doses which led to maximal plasma concentrations (C_{max}) of the drug in the range of the *in vitro* IC_{50} value, thus indicating a potential risk to patients for serious adverse cardiac events. However, buccal administration at the same doses and similar, if not higher C_{max} values did not result in any prolongation of the QTc. Since this finding cannot be judged therefore to be due to differences in exposure to the parent drug, the elimination of the cardiac risk (QTc prolongation) by using the buccal route of dosing instead of the oral route has to be considered unexpected and a finding that could not have been predicted from the properties of the compound. On the contrary, using common toxicological reasoning, it would have been predicted that the buccal route, which avoids first pass metabolism of a compound in the liver, should have elicited a more extensive effect of the drug substance on cardiac safety parameters such as the QT interval than the one observed with oral dosing.

In conclusion, this expert is of the firm opinion that, for a number of reasons, the lack of influence on cardiac depolarization and repolarization parameters, specifically the QTc interval, observed under the conditions of buccal application, and which is in stark contrast to the significant and dose-related increases in QTc observed with oral dosing, could not have been foreseen through the use of toxicological knowledge and experience, taking into account common toxicological principles and based upon the available data on the toxicological properties of fipamezole. Since QT interval prolongation is an effect that would lead to the abandonment of the development of a pharmaceutical substance, the unexpected finding that a change in the route of administration (which for fipamezole does not change the systemic exposure to the active pharmaceutical entity) can certainly abrogate the importance of the QT interval prolongation (as observed in orally treated dogs) for the human situation.

Consequently, and in view of this unexpectedness of the finding, the buccal route of administration should certainly be considered to be novel and non-obvious.

The QT-Interval in the Electrocardiogram

The electrocardiogram (ECG) is a graphic representation of the electrical processes occurring and signals generated in the heart during its contraction and relaxation phases. The ECG is the sum of the electrical signals that originate from the changes in the membrane polarization (voltage difference between the inside and the outside) of the cardiac muscle cells, the cardiomyocytes, during a heart beat. The most commonly utilized form of the ECG is derived from the so-called "lead II" in which the various peaks are most distinctly expressed and therefore most easily analyzed. These peaks (see figure 1) are labeled with the letters P, Q, R, S and T and correspond to the different phases of the electrical excitation and repolarization of the heart: The P wave corresponds to the atrial excitation, the QRS complex to the ventricular excitation, the T wave to the ventricular repolarization and the distance between two sequential R peaks (the RR interval) to the interval between two heartbeats. The repolarization of the ventricular myocytes returns them to the resting state, from which they can then be excited again. Only if the ventricle is fully repolarized before the start of a new polarization-repolarization sequence can it react to the electrical impulses generated in the so-called "pacing" area of the atria in an orderly way.

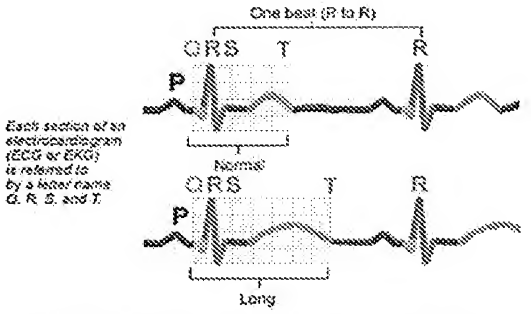

Figure 1: Electrocardiogram with upper panel showing 'normal' QT interval and lower panel showing 'long' QT interval, or QT prolongation

The QT interval (time from the beginning of the QRS complex to the end of the T wave) is thus a measure of the duration of ventricular excitation and subsequent repolarization. A normal QT interval is less than half the RR interval. The absolute length (in milliseconds) of this interval is however dependent on the heart rate: A lower heart rate (increased RR interval) will increase the QT interval, while a higher rate will shorten it. Therefore, the QT interval measured from the ECG should be corrected for the concurrent heart rate (QTc). Several correction methods are known: Bazett's correction, the oldest and most frequently used, leads to an overestimation of the QTc; the more recent Fridericia's correction yields relatively reliable values, whilst the Van de Water correction is most specifically adapted to dogs and is thus frequently used for evaluations in this species.

Ventricular depolarization and repolarization are complex physiological processes. They arise from the net activities of many membrane ion channels and transporters. The rapidly and slowly activating components of the delayed rectifier potassium current, IKr and IKs, seem to have the most influential role in determining the duration of the QT interval. The most common mechanism of QT interval

prolongation by drug molecules is inhibition of the potassium current through the delayed rectifier potassium channel. This membrane potassium channel is the protein product of the human ether-a-go-go-related gene (hERG). Consequently, the primary assays for QT interval-prolonging properties of drug substances are *in vitro* tests measuring the inhibition of the potassium ion current through this channel in mammalian cell lines expressing the hERG gene, as required by internationally accepted guidelines such as ICH S7B "Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" and incorporated into the FDA Guidance for Industry series (October 2005). In this assay the concentration of the test substance at which a 50% inhibition (IC_{50}) of the potassium current is observed is thereby the standard value based on which the evaluation of the potential for a cardiac risk is made.

Consequence of the QT / QTc Interval Prolongation

When the QTc interval is increased, repolarization of the heart muscle cells is delayed. This delay can ultimately lead to a condition where the ventricular cardiomyocytes are not yet fully repolarized (i.e., have not yet reached the original "resting state" with the normal resting voltage across their cell membranes) when the next signal for depolarization arrives from the atrial pacemaker region. Under this condition, the excitation wave cannot be propagated correctly throughout the ventricle, and there is consequently an increased risk of adverse cardiac events, such as ventricular tachyarrhythmia, including torsade de pointes (see figure 2), ventricular fibrillation and ultimately cardiac arrest. Figure 3 overleaf shows another example, where the longer than normal QT interval leads to tachycardia and torsade de pointes (reduction in the amplitude of the QRS complex and even reversal of polarity in this complex), before the heart rate normalizes again.

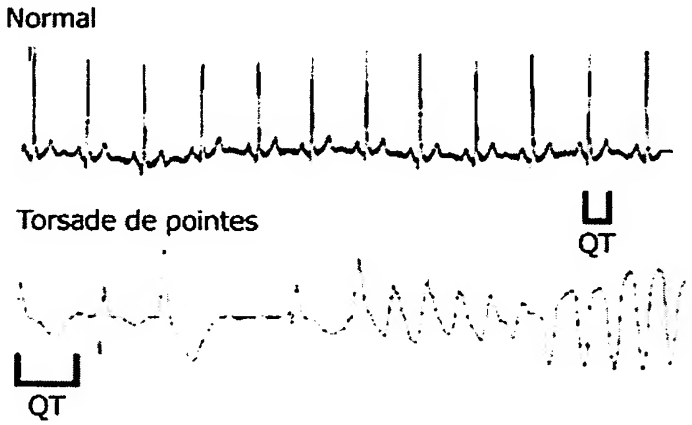

Figure 2: ECG trace showing ventricular tachyarrhythmia and Torsade de Pointes

Consequently, any drug that exhibits QT interval prolonging effects has to be considered to increase the risk of lethal cardiac complications. A number of drugs that have been shown to cause QT interval prolongation (e.g., terfenadine, astemizole, cisapride, and grepafloxacin) have been withdrawn from the market because of the cardiac risk associated with this effect.

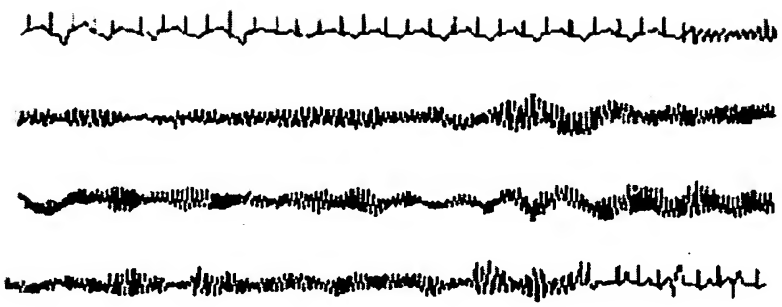

Figure 3: Lead-II ECG (recorded for 2 minutes) showing the onset of tachyarrhythmia (right end of upper trace) and torsade de pointes (second trace till end of lowest trace) reverting to a normal heart rate after some time.

If, in the course of drug development, either in non-clinical studies or in clinical trials, a candidate drug is found to induce QT interval prolongation, the further development of this particular substance may be abandoned. However, if it can be demonstrated that the QT interval prolongation depends on specific conditions that can be avoided in the therapeutic situation, so that the cardiac risk can be minimized, such a substance may still be developed further and become marketed. The determination of the potential of a candidate drug substance to induce QT interval prolonging effects is therefore of utmost importance, and high emphasis is placed on the accurate assessment of this parameter in the non-clinical investigation programme, most specifically by using telemetry to study the ECG in the conscious freely moving dog.

QTc Intervals Determined in Studies with Fipamezole in the Dog

Electrocardiograms have been recorded in a number of non-clinical studies in dogs treated with fipamezole and have provided the following results.

In a safety pharmacology study, fipamezole was administered to conscious, freely moving telemetered dogs in single doses of 1, 5 and 10 mg/kg by buccal spray. There were no ECG effects of fipamezole dosing on P wave amplitude, P wave duration, PQ interval, QRS interval, or QTc interval.

In a 1 month toxicity study fipamezole was given daily to dogs orally in capsules at doses of 5, 10 and 15 mg/kg/day. ECGs were recorded pre-test (before the first dose) and both before dosing and 1 hour post dosing on days 1 and 29. The table below shows QTc intervals calculated from QT intervals recorded pre-test and on day 29:

	QTc (msec) - mean of males and females					
Correction	Van de Water	Fridericia	Van de Water	Fridericia	Van de Water	Fridericia
Dose group	pretest		Day 29, predose		Day 29, 1 hr post-dose	
control	227.83	228.81	226.13	225.96	226.90	227.63
5mg/kg	225.02	226.93	234.74	235.93	230.76	233.94
10 mg/kg	224.92	228.56	249.52	252.45	242.28	245.34
15 mg/kg	224.41	224.00	257.21	259.39	245.31	246.97

From these values it is evident that the treatment with fipamezole induced a significant and dose-related prolongation of the corrected QT interval on day 29 of the study; an effect that was apparent in both the predose and 1 hour post dose recordings.

In another 1 month toxicity study in dogs, fipamezole was administered by buccal spray in doses of 1, 5 and 10 mg/kg/day. Again, ECGs were taken pre-test as well as on days 1 and 29 before and 1 hour after dosing. The table below shows QTc calculated from QT intervals recorded pre-test and on day 29:

	QTc (msec) - mean of males and females					
Correction	Van de Water	Fridericia	Van de Water	Fridericia	Van de Water	Fridericia
Dose group	pretest		Day 29, predose		Day 29, 1 hr post-dose	
control	238.34	241.30	222.68	223.84	229.25	231.05
1 mg/kg	242.94	250.32	225.50	228.78	227.99	228.48
5 mg/kg	234.22	240.65	224.02	226.20	227.87	229.11
10 mg/kg	232.80	235.51	226.52	229.24	229.54	230.35

From the values presented above it is clear that in this study, where fipamezole was dosed buccally, no changes whatsoever in QTc interval have occurred.

Systemic exposure to fipamezole was determined in both of these toxicity studies and have yielded the following maximal plasma concentrations (only those at comparable doses are given here):

	oral C_{max} (ng/ml)			buccal C_{max} (ng/ml)		
	M	F	mean	M	F	mean
Day 1						
5 mg/kg	2338.7	1656.9	1997.8	2561.9	2794.7	2561.9
10 mg/kg	3445.4	2702.3	3073.8	6843.8	4311.6	5577.7
Day 28						
5 mg/kg	1039.4	857.0	948.2	1104.7	481.5	793.1
10 mg/kg	1566.6	1767.0	1666.8	1976.7	591.7	1284.2

It is evident that buccal dosing with oromucosal absorption of fipamezole does lead to as high, or even higher, C_{max} values than oral dosing with subsequent gastrointestinal absorption. This is a well known, and expected, phenomenon, because after its gastrointestinal absorption a drug substance is taken up into the portal vein and has consequently to pass first through the liver, an organ in which most of the metabolic reactions take place, before it enters into the systemic circulation. This "first-pass" conversion to metabolites will consequently decrease the amount of unaltered drug substance to be measured in the peripheral blood plasma. Contrary to this, any mode of application whereby the drug enters into the systemic circulation in bypassing the liver, such as intravenous, subcutaneous and buccal dosing, will yield higher initial concentrations of the drug in the peripheral blood, with metabolism occurring in a protracted manner.

Additional Data on Potential Cardiac Effects of Fipamezole

As required by internationally accepted guidelines, *in vitro* safety pharmacology studies have also been conducted with fipamezole for the investigation of its potential to influence cardiac depolarization and repolarization. These studies had been performed prior to the *in vivo* toxicity studies in order to obtain preliminary information about potential liabilities of the compound as well as to form the basis for determining the necessity to conduct any special investigations within these *in vivo* studies.

In these, an *in vitro* assay for inhibition of the potassium current through the hERG channel demonstrated a concentration-related increase in the inhibition of the potassium current through the hERG channel with an 80% inhibition measured at the maximum concentration tested in the assay of 30 µM (6.9 µg/ml). The inhibitory potential of fipamezole on the hERG channel is characterized by an IC_{50} of 9.56 µM (2.2 µg/ml).

Summary

In a one month toxicity study, oral administration of fipamezole to dogs was shown to result in a dose-related prolongation of the corrected QT interval (QTc). As is common practice in drug development, drug effects seen in animal toxicology studies are extrapolated to man. Based on this, the fipamezole-induced effect on QTc interval in dogs indicates that a potential risk exists for the drug to induce serious adverse events in treated patients.

Whilst this risk is apparent when fipamezole is dosed via the oral route, no such similar effect has been observed when fipamezole was given via the buccal route, as shown in both a 1 month toxicity study as well as a single dose dog telemetry study. The toxicokinetic data provide evidence, that in the two studies, similar systemic exposures (C_{max}) were reached by both, the oral and the buccal routes. This difference in effect on the ECG is therefore not due to any differences in exposure to the parent drug. Consequently, elimination of the cardiac risk (QTc prolongation) by using the buccal route of dosing instead of the oral route has to be considered unexpected and a difference that could not have been predicted from the properties of the compound.

It is to be recognized that QT prolongation can lead to serious adverse events and is thus a property of a candidate substance that would either hinder, or preclude the further development to a marketed drug. In many cases, the expression of this property in clinical populations has already led to the withdrawal of registered compounds from the market. In addition an unknown number of promising pharmaceutical active ingredients have been withdrawn from further development because of non-clinical and clinical evidence that the observed hazard of QT interval prolongation might be extrapolatable to a concrete risk to patients for the induction of lethal arrhythmias.

In the case of fipamezole, however, this property is expressed only if the compound is administered by the oral route, while at the same doses and at similar, if not higher, systemic exposures, the buccal route is devoid of this effect. Considering the sum of prior knowledge about the biological, toxicological and pharmacokinetic properties of this substance, it could not have been foreseen or predicted that the buccal route

would be of lesser concern for this serious adverse event. On the contrary, it would have been predicted that the buccal route, which avoids first pass metabolism of a compound in the liver, should have exhibited a more extensive effect of the drug substance on the cardiac safety parameters, such as the QT interval.

Conclusions

In conclusion, it is the opinion of this expert, that the lack of a QT interval prolonging effect of fipamezole when administered by the buccal route, in contrast to the clear effect elicited when administered by the oral route, could not have been predicted from the properties of the substance as they were known before the start of the respective study.

Since QT interval prolongation is an effect that would lead to the abandonment of the development of a pharmaceutical substance, the unexpected finding that a change in the route of administration (which for fipamezole does not change the systemic exposure to the active pharmaceutical entity) can certainly abrogate the importance of the QT interval prolongation (as observed in orally treated dogs) for the human situation. Consequently, and in view of this unexpectedness of the finding, the buccal route of administration should certainly be considered to be novel and non-obvious.